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Health and Environmental Effects Profile for 4-Vinyl-1-Cyclohexene

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR 4-VINYL-1-CYCLOHEXENE

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16. ABSTRACT

The Health and Environmental Effects Profile for 4-Vinyl-1-cyclohexene was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for 4-Vinyl-1-cyclohexene.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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EXECUTIVE SUMMARY

4-Vinyl-1-cyclohexene is a flammable liquid at room temperature. The compound is prepared by the dimerization of butadiene. It is commercially produced as a by-product during butadiene manufacture; is mainly used as an intermediate in the manufacture of polymers. 4-Vinyl-1-cyclohexene has been detected in the air and wastewater of rubber vulcanization operations. However, environmental fate and transport processes of this compound have not been investigated experimentally, although some estimates are available based on physical parameters.

Lethal dose studies with rats indicate a low level of toxicity for 4-vinyl-1-cyclohexene following acute oral (LD_{50} ~2.6 g/kg) and inhalation (LC_{50} ~8000 ppm) exposure. When administered dermally high doses of the compound will cause mortality in rabbits (LD_{50} ~16.6 g/kg), and topical application of the undiluted compound has caused local skin (moderate) and corneal (mild) irritation. According to Russian studies, intermittent daily inhalation exposure at a level of ~226 ppm has been reported to inhibit weight gain and cause hematologic effects in rats and mice after 4 months, but the validity of these results is uncertain. Undetailed reports of effects in humans suggest that local skin and mucous membrane irritation, central nervous system effects and hematologic effects may result from occupational exposure.

The results of a lifetime skin painting study in mice suggest a positive local tumorigenic effect of 4-vinyl-1-cyclohexene, but this response may have been caused by the presence of a carcinogenic auto-oxidation product (4-hydroperoxy-4-vinyl-1-cyclohexene). 4-Vinyl-1-cyclohexene has not been tested for mutagenicity (or teratogenicity or reproductive effects).

Testing of its mono epoxide metabolites in the Ames assay has given both positive and negative results. The diepoxide derivative has been reported to be both carcinogenic and mutagenic, but *in vitro* metabolism to the diepoxide appears to be negligible.

1. INTRODUCTION

4-Vinyl-1-cyclohexene (4-ethenyl-1-cyclohexene, 1,2,3,4-tetrahydrostyrene) is a flammable liquid at room temperature. The compound can be prepared by the dimerization of butadiene at high temperature and pressure or in the presence of catalysts (IARC, 1976). It is commercially produced as a by-product during butadiene manufacture (IARC, 1976).

CAS Registry Number	100-40-3
Formula	$C_6H_9 - CH = CH_2$
Molecular Weight	108.2
Melting Point	-108.9°C (Hawley, 1977)
Boiling Point	128°C (Hawley, 1977); 129°C (Varushchenko et al., 1974)
Specific Gravity	(20/4°C): 0.8303 (Hawley, 1977)
Flash Point	21.1°C (Hawley, 1977)
Vapor Pressure	364 mm at 20°C (Varushchenko et al., 1974) 10 mm at 20°C (Mabey et al., 1982)
Solubility	at 25°C: 50 mg in 1000 g of water (McAuliffe, 1966); 95 mg/ℓ (Mabey et al., 1982)
Log octanol-water partition coefficient (calculated)	3.48 (Mabey et al., 1982)

4-Vinyl-1-cyclohexene is produced in the United States by Neochem. Corp., Arcadia, Texas, and Union Carbide Corp., Institute, West Virginia (SRI, 1981). The yearly production of this chemical in the United States is probably >454 kg (SRI, 1975).

4-Vinyl-1-cyclohexene is used as an intermediate for the production of 4-vinyl-1-cyclohexene dioxide, which is used as a reactive diluent in epoxy resin. Although small amounts of 4-vinyl-1-cyclohexene may also have been used as a co-monomer in the polymerization of other monomers (namely, styrene) and halogenation to polyhalogenated derivatives used as flame retardants, no evidence was found to indicate that it is now being used in such applications (IARC, 1976).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

The environmental fate and transport processes of this compound have not been investigated experimentally. However, some tentative predictions can be made from fundamental data presented in Chapter 1. Mackay and Wolkoff (1973) have shown that the Henry's constant (H_c) for a given chemical equals its vapor pressure divided by its solubility provided the data are for the pure material in the same phase at the same temperature. The Henry's constant for 4-vinyl-1-cyclohexene calculated by this method then equals 0.55 atm. m^3/mole if the experimental vapor pressure of Varushchenko et al. (1974) is accepted. If instead the boiling point (129°C) reported by Varushchenko et al. (1974) is used to calculate vapor pressure (10 torr) at the same temperature (20°C) by a method reported by Mackay et al. (1982) then the Henry's constant appears to be in the range of 0.015 atm. m^3/mole. These values might be compared to a Henry's constant of 5.5×10^{-3} atm. m^3/mole for benzene reported by Mackay and Leinonen (1975) who also estimated the evaporative half-life of benzene from a 1 m depth of water as ~5 hours. Given either value of H_c, we might anticipate by comparison that 4-vinyl-1-cyclohexene would volatilize from aquatic media more readily than benzene, particularly from turbulent water bodies.

The partition coefficient for 4-vinyl-1-cyclohexene sorption on sediment from aquatic media can be calculated using a correlation equation proposed by Schwarzenbach and Westall (1981) and the octanol/water partition coefficient of 3.48 calculated by Mabey, et al. (1982). The calculated value equals 4.9 for a sediment containing 0.5% organic carbon. The log K_{oc} value which may be calculated from a second equation presented by Schwarzenbach and Westall (1981) equals 3.00, somewhat larger than an experimental log K_{oc} of 2.60 reported for tetrachloroethylene by the same authors. It

has been reported that tetrachloroethylene is not significantly adsorbed to sediments containing low organic matter, whereas sediments rich in organic matter may show higher sorption capacity (Callahan et al., 1979). The transport of 4-vinyl-1-cyclohexene from the aquatic phase to sediments is expected to be slightly greater than that observed for tetrachloroethylene.

This compound is not expected to undergo direct photolysis in aquatic media because it is not anticipated to absorb light of >300 nm wavelength (Mabey et al., 1982).* Oxidation of this compound in water by peroxyl radicals (RO_2) (indirect photolysis) is expected to proceed very slowly. For a saturated solution the calculated half-life is in the range of a few years, based on a rate constant of 7 M^{-1} sec^{-1} (Mabey et al., 1982) and an estimated peroxyl radical concentration of 10^{-9}M in aquatic media (Mill et al., 1980). A second process, involving oxidation by singlet oxygen, should dominate since the saturated solution half-life is in the range of a week based on a calculated rate constant of 10^4 M^{-1} sec^{-1} (Mabey et al., 1982) and a singlet oxygen concentration in sunlit waters of ~10^{-12} M (Zepp et al., 1978).

No experimental information was found regarding the microbial degradability of 4-vinyl-1-cyclohexene in the aquatic environment or soils. However, assuming an estimated microbial degradation rate constant of 10^{-10} mℓ $cell^{-1}$ $hour^{-1}$ (Mabey et al., 1982) and the concentration of microorganisms in aquatic media as $5x10^5$ cell $mℓ^{-1}$ (Burns et al., 1981), biodegradation of this compound in the aquatic phase does not appear to be a significant fate process.

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*Mabey et al. (1982) caution that their estimated rate constants and calculated physical parameters were intended only for determining the relative contributions of potential degradation or dissipation mechanisms and should not be used to determine absolute rates without further consultation with the authors.

3. EXPOSURE

One Russian study (IARC, 1976) reported the average concentration of 4-vinyl-1-cyclohexene at its manufacturing site to be 1.2-2.4 g/m^3, with a maximum concentration of 3.0 g/m^3. In the United States, Rappaport and Fraser (1977) detected 0.313 and 0.408 mg/m^3 of 4-vinyl-1-cyclohexene in two areas of a passenger tire curing room. The 4-vinyl-1-cyclohexene probably originated from polylbutadiene rubber used in tire manufacture. Rappaport (1975) also identified 4-vinyl-1-cyclohexene in the effluents from rubber vulcanization. It was also detected in the Mississippi River, LA, originating from chemical effluents (Shackelford and Keith, 1976). No other data are available on the environmental level of this compound in any other media.

4. PHARMACOKINETICS

4.1. ABSORPTION

Pertinent data regarding the absorption of 4-vinyl-1-cyclohexene could not be located in the available literature.

4.2. DISTRIBUTION

Pertinent data regarding the distribution of 4-vinyl-1-cyclohexene were not located in the available literature.

4.3. METABOLISM

4-Vinyl-1-cyclohexene was oxidized by rat liver microsomes at either double bond to the monoepoxide, and subsequently was hydrolyzed to the corresponding diol (Watabe et al., 1981). Preferential epoxidation occurred at the ring double bond (3.5-fold greater than at the vinyl double bond), but diepoxide formation (1-ethylenoxy-3,4-epoxycyclohexane) was not detected.

Rapid depletion of hepatic reduced glutathione in mice following the administration of 500 mg/kg 4-vinyl-1-cyclohexene, 4-vinyl-1-cyclohexene monoxide or 4-vinyl-1-cyclohexene diepoxide suggests that glutathione is probably involved in the metabolism of 4-vinyl-1-cyclohexene (Giannarini et al., 1981).

4.4. EXCRETION

Pertinent data regarding the excretion of 4-vinyl-1-cyclohexene were not found in the available literature.

5. EFFECTS

5.1. CARCINOGENICITY

The carcinogenic potential of topically administered 4-vinyl-1-cyclohexene was evaluated in male 8-week-old Swiss-Millerton mice (Van Duuren et al., 1963). When 45 mg of the compound in benzene was applied to the clipped dorsal skin of 30 mice 3 times/week for life, it was found that 6 developed skin tumors, and that 1 of the 6 tumors was a squamous cell carcinoma. The median survival time was 375 days; extensive skin damage was also associated with administration of 4-vinyl-1-cyclohexene. Of 150 control mice painted with benzene alone (100 mg/application), 10 developed skin papillomas and 1 developed a carcinoma. The increased tumor incidence in the treated mice was reported by IARC (1976) to be significant ($P<0.02$).

The 4-vinyl-1-cyclohexene tested in this experiment was commercial grade that was purified by removal of auto-oxidation products with ferrous sulfate, followed by distillation in a nitrogen atmosphere. Van Duuren et al. (1963) have suggested, however, the possibility that the 4-vinyl-1-cyclohexene tested may have contained a minute amount of hydroperoxide (4-hydroperoxy-4-vinyl-1-cyclohexene) formed by auto-oxidation; the hydroperoxide showed definite carcinogenic activity in two similarly designed skin painting studies. The possibility of contamination influence was examined in a subsequent experiment that utilized the hydrocarbon freed from auto-oxidation products by treatment with ferrous sulfate before use (Van Duuren, 1965). When 100 mg of "oxygen-free" 4-vinyl-1-cyclohexene in benzene was applied to the skin of 30 male Swiss mice 3 times/week for life, the median survival time was 565 days, and no carcinogenic effect was observed.

The diepoxide derivative of 4-vinyl-1-cyclohexene (1-ethylenoxy-3,4-epoxycyclohexane) has elicited positive carcinogenic responses in rats and mice following intraperitoneal (i.p.) injection and skin application (Rose et al., 1950; Hendry et al., 1951; Van Duuren et al., 1963). The significance of these findings is uncertain, however, because *in vivo* metabolism to the diepoxide may be negligible (see Chapter 4.3.).

A carcinogenesis bioassay of 4-vinyl-1-cyclohexene is currently being conducted by the National Toxicology Program (NTP, 1982); rats and mice are being administered the compound via gavage and chronic testing is in progress.

5.2. MUTAGENICITY

4-Vinyl-1-cyclohexene has not been tested for mutagenicity. The monoepoxide derivatives were tested in the Ames *Salmonella* assay, but reportedly showed no mutagenic activity to strains TA98, TA100, TA1535, TA1537 or TA1538 when tested at concentrations of 0.1, 1.0 or 10 µmol/plate in the presence or absence of rat liver homogenate S-9 fraction (Watabe et al., 1981). In the absence of metabolic activation at a concentration of 10 µmol/plate, however, the diepoxide derivative was mutagenic to *S. typhimurium* TA100.

Simmon and Baden (1980) obtained dose-related increases in revertants in *S. typhimurium* TA1535, TA98 and TA100 in the presence of S-9 activation using the same monoepoxide derivatives. These metabolites also induced dose-related increases in revertants in TA1535 and TA100 in the absence of S-9 metabolic activation. The discrepancy with Watabe et al. (1981) might be because the latter authors did not take sufficient precaution in handling the volatile monoepoxides.

An additional paper by Turchi et al. (1981) further demonstrates that many of these epoxymetabolites of 4-vinyl-1-cyclohexene induce gene mutations and chromosomal aberrations (anaphase bridges, lagging chromosomes and micronuclei) in Chinese hamster V79 cells.

Although mutagenicity data on 4-vinyl-1-cyclohexene are lacking, the reported studies suggest that some of its metabolites are mutagenic. Thus, the parent compound may have the potential to be mutagenic.

5.3. TERATOGENICITY

Information on the teratogenicity or embryotoxicity of 4-vinyl-1-cyclohexene was not found in the available literature.

5.4. OTHER REPRODUCTIVE EFFECTS

Information on the reproductive effects of 4-vinyl-1-cyclohexene was not found in the available literature.

5.5. CHRONIC TOXICITY

Information on the effects of chronic exposure to 4-vinyl-1-cyclohexene in animals was not found in the available literature.

Inhalation of 1000 mg/m^3 (~226 ppm) 4-vinyl-1-cyclohexene for 6 hours/day for 4 months reportedly inhibited weight gain and caused leukocytosis, leukopenia and hemodynamic impairment in rats and mice (Bykov, 1968). Additional details of this Russian study are not available.

Bykov (1968) also reported that keratitis, rhinitis, headache, hypotonia, leukopenia, neutrophilia, lymphocytosis and impairment of pigment and carbohydrate metabolism were noted in Russian workers exposed to 4-vinyl-1-cyclohexene.

5.6. ACUTE TOXICITY

Limited information is available on the acute toxic effects of 4-vinyl-1-cyclohexene. As detailed in Table 5-1, most of the data on this compound

TABLE 5-1

Acute Lethal and Irritant Effects of 4-Vinyl-1-Cyclohexene

Route	Species/Strain	Sex	Number	Vehicle	Dosage	Response	Reference
Oral (gavage)	rat/Carworth-Wistar	Male	5/group	NS[a]	2.56 g/kg[b] (2.07-3.16)	Range-finding LD_{50} (14-days)	Smyth et al., 1969
Inhalation	rat/NS	NS	6/group	NS	8000 ppm[c,d] x 4 hours	2 of 6 died within 14 days	Smyth et al., 1969
Inhalation	rat/albino	NS	6/group	NS	concentrated vapor x 15 minutes[e]	maximum time for 6 rats to survive 14 days	Smyth et al., 1969
Inhalation	rat/NS	NS	NS	NS	10,621 ppm	LC_{50}	Bykov, 1968
Inhalation	mouse/NS	NS	NS	NS	6101 ppm	LC_{50}	Bykov, 1968
Dermal	rabbit/albino New Zealand	male	4/group	NS	16.61 g/kg, single dose occluded 24 hours contact	range-finding LD_{50} (14-days)	Smyth et al., 1969
Dermal	rabbit/albino	NS	5	undiluted	0.01 mℓ (8.3 mg), uncovered application	slight erythema (Grade 4)	Smyth et al., 1969
Ocular	rabbit/albino	NS	5 eyes	undiluted	0.5 mℓ (0.42 kg), corneal application	mild irritation after 18-24 hours (Grade 2)	Smyth et al., 1969

[a]Not specifically stated if the chemical was administered undiluted (NS = Not specified)

[b]Groups of 5 rats administered logarithmic series of doses that differed by a factor of 2.

[c]Nominal concentration

[d]Logarithmic series of concentrations that differed by a factor of 2.

[e]Groups of 6 rats exposed for a logarithmic series of time intervals that differed by a factor of 2.

was generated in range-finding toxicity and irritation studies conducted by Smyth et al. (1969). The data indicate that high concentrations of 4-vinyl-1-cyclohexene are needed to produce mortality in rats following single oral, dermal or short-term vapor exposure. Single topical applications of the undiluted compound produce moderate skin irritation and mild corneal irritation in rabbits.

Sandmeyer (1981) notes that 4-vinyl-1-cyclohexene is probably an irritant and a central nervous system depressant at high concentrations.

5.7. OTHER RELEVANT INFORMATION

Additional relevant information concerning 4-vinyl-1-cyclohexene was not found in the available literature.

6. AQUATIC TOXICITY

6.1. ACUTE AND CHRONIC TOXICITY

Pertinent data regarding the acute or chronic toxicity of 4-vinyl-1-cyclohexene to aquatic animals or plants were not located in the available literature.

6.2. RESIDUES

Pertinent data regarding residues of 4-vinyl-1-cyclohexene in aquatic media were not located in the available literature. However, Veith et al. (1980) suggest the use of the following equation to estimate bioconcentration factor (BCF) from the octanol-water partition coefficient (K_{ow}):

$$\log BCF = 0.76 \log K_{ow} - 0.23$$

Using this equation and the estimated log K_{ow} (3.48) from Section 1, the BCF for whole fish is calculated to be ~260.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

No formally recommended or promulgated ambient or occupational exposure standards or guidelines were found for 4-vinyl-1-cyclohexene. Sandmeyer (1981) noted, however, that it has been suggested that the vapor concentration of this substance be kept below 100 ppm in any workroom environment. The basis for this suggestion was not discussed.

7.2. AQUATIC

Pertinent data regarding existing guidelines and standards for 4-vinyl-1-cyclohexene were not located in the available literature.

8. APPROACHES TO RISK ASSESSMENT

4-Vinyl-1-cyclohexene was tested for carcinogenicity in mice by lifetime skin application and initial results indicated a significant local tumorigenic response (Van Duuren et al., 1963). The possibility of low-level contamination with the carcinogenic auto-oxidation product 4-hydroxy-4-vinyl-1-cyclohexene was suggested, however, and retesting with "oxygen free" 4-vinyl-1-cyclohexene reportedly showed no carcinogenic effect (Van Duuren, 1965). 4-Vinyl-1-cyclohexene has not been tested for mutagenicity, but testing of its monoepoxide metabolite in the Ames assay has been reported to be negative (Watabe et al., 1981) or positive (Simmon and Baden, 1980). The diepoxide derivative has been reported to be carcinogenic in rats and mice following i.p. injection or skin application (Rose et al., 1950; Hendry et al., 1951; Van Duuren et al., 1963) and mutagenic to S. typhimurium TA100 at high doses (Watabe et al., 1981), but in vitro metabolism to the diepoxide did not occur or was negligible (Watabe et al., 1981). The mutagenic and carcinogenic potential of 4-vinyl-1-cyclohexene is therefore uncertain, and the equivocal mouse skin painting results of Van Duuren et al. (1963) and Van Duuren (1965) cannot be used as a basis for quantitative risk assessment.

Reliable toxicity data for 4-vinyl-1-cyclohexene is otherwise limited to acute lethal dose determinations in rats (oral and inhalation exposure) and rabbits (dermal exposure) (Smyth et al., 1969). These data indicate a low level of acute systemic toxicity, but cannot (alone) be used to derive an acceptable daily intake (ADI). Inhalation of ~200 ppm 4-vinyl-1-cyclohexene for 6 hours/day for 4 months was reported in the proceedings of a Russian conference (Bykov, 1968) to have inhibited weight gain and elicited various hematologic effects in rats and mice, but additional information necessary for justification of an ADI derivation was not provided.

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